201-16613B

Revised Robust Summaries for

IRGANOX 1035

Melting Point
Water Solubility
Hydrolysis
Fugacity
Genetic Toxicity In vitro
Developmental Toxicity
Reproduction Toxicity

Thiodiethylene bis (3, 5-di-tert-butyl-4-hydroxyhydrocinnamate)

CAS No. 41484-35-9

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PHYSICAL/CHEMICAL ELEMENTS

1. MELTING POINT *(Revised)*

Test substance:	Thiodiethylene bis (3,5-di-tert-butyl-4-hydroxyhydro cinnamate) CAS No. 41484-35-9
Method:	EQC model v 1.0
GLP:	No
Year:	5/30/01
Results:	63 °C
Remarks:	The melting point was calculated using an accepted method (The EQC model v 1.0) and assigned a reliability code of 2f [1] (Accepted calculation method).
References:	[1]Klimisch, H.J., Andreae, M and Tillman, U., A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology.* 25:1-5, 1997.

WATER SOLUBILITY ***(Revised)***

Test substance:	Thiodiethylene bis (3,5-di-tert-butyl-4-hydroxyhydro cinnamate) CAS No. 41484-35-9
Method:	A series of experiments were conducted to evaluate the water solubility of Irganox 1035. A stock solution of Irganox 1035 was prepared and dilutions were made ranging from 9 ppb to 40 ppb. Each solution was shaken overnight and extracted 2 times with 150 ml of methylene chloride and the extracts were evaporated under nitrogen. The dried material was reconstituted in 1.0 ml of ethyl acetate / aceonitrile, sonicated and vortexed. The reconstituted material was analyzed for the test substance using high pressure liquid chromatography. This approach showed Irganox 1035 reached a maximum solubility of 7 ppb. A second approach used to measure the water solubility involved concentration of spiked water samples using a solid phase extraction device (SPE). The SPE selectively removed the test compound from the water and concentrated the sample. Water samples were spiked with Irganox 1035 at several concentrations ranging form 10 – 80 ppb. The results showed that the absolute concentration of Irganox 1035 in the water was consistently around 5 ppb indicating this was the limit of solubility.
GLP:	No
Year:	2006
Results:	The solubility of Irganox 1035 is 5-7 ppb.
Remarks:	This study was assigned a reliability code of 2b [2] (comparable to a guideline study).
References:	Water Solubility Testing for Irganox 1035. Analytical Chemistry Department, Tarrytown, NY. [2] Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology.* 25:1-5, 1997.

ENVIRONMENTAL FATE AND PATHWAYS ELEMENTS

STABILITY IN WATER / HYDROLYSIS ***(Revised)***

Test substance:	Thiodiethylene bis (3, 5-di-tert-butyl-4-hydroxyhydro cinnamate) CAS No. 41484-35-9
Method:	HYDROWIN Program (v. 1.67) [1,2] plus technical discussion
GLP:	No
Year:	2006
Results:	The HYDROWIN Program was unable to evaluate the fragments of this chemical structure. This material has very low water solubility (5-7 ppb) and hydrolysis can not be practically evaluated.
Discussion:	Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals with no leaving group render a compound resistant to hydrolysis. Therefore, Irganox 1035 is resistant to hydrolysis because it lacks functional groups like esters, carbamates and other groups which are hydrolytically reactive. The Aqueous Hydrolysis Rate Program (HYDROWIN) estimates aqueous hydrolysis rate constants for the following chemical classes: esters, carbamates, epoxides, halomethanes and selected alkyl halides. HYDROWIN estimates acid- and base-catalyzed rate constants; it does not estimate neutral hydrolysis rate constants. The program is therefore ineffective for Irganox 1035.
Remarks:	The estimate was assigned a reliability code of 2[3] because it is a technical discussion and not a study.
References:	[1]Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998. [3]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology.* 25:1-5, 1997.

THEORETICAL DISTRIBUTION (FUGACITY CALCULATION) ***(Revised)***

Test substance:	Thiodiethylene bis (3, 5-di-tert-butyl-4-hydroxyhydro cinnamate) CAS No. 41484-35-9
Method:	Estimated by EPIWIN Level III Fugacity Model.[1, 2] Input for the model is the SMILES structure of the molecule. All other input values are calculated by EPI-WIN.
Year:	2006
GLP:	No
Results:	Distribution using EQC Level III Fugacity Model Air 0.00046 % Water 1.04 % Soil 44.4 % Sediment 54.6 % Persistence Time = 7.4×10^3 h
Remarks:	In the absence of reliable experimental data, the fugacity was calculated using an accepted method and assigned a reliability code of 2f [3] (Accepted calculation method).
References:	[1]Syracuse Research Corporation, Syracuse, NY [2]Pollution Prevention (P2) Assessment Framework, U.S. Environmental Protection Agency, Office of Pollution Prevention and Toxics (Draft), 1998. [3]Klimisch, H.J., Andreae, M and Tillman, U. A systemic approach for evaluating the quality of experimental toxicological and ecotoxicological data. *Regulatory Toxicology and Pharmacology.* 25:1-5, 1997.

GENETIC TOXICITY IN VITRO ***(Revised)***

Test substance: Thiodiethylene bis (3,5-di-tert-butyl-4-hydroxyhydro cinnamate)
CAS No. 41484-35-9

Chromosomal Aberration Test:

Irganox 1035 is structurally related to several hindered phenol antioxidants also involved in the HPV program, notably CAS 2082-79-3, CAS 6683-19-8 and CAS 32687-78-8 (these chemicals are also sponsored by Ciba Specialty Chemicals Corporation). Cytogenic testing for these substances has demonstrated that the compounds are not clastogenic. Additional supporting data relating to hindered phenol antioxidants has been presented for the HPV Hindered Phenol Category, sponsored by the American Chemistry Council. These data indicate a low concern for clastogenic effects.

DEVELOPMENTAL TOXICITY ***(Revised)***

Test substance:	Thiodiethylene bis (3,5-di-tert-butyl-4-hydroxyhydro cinnamate) CAS No. 41484-35-9

Irganox 1035 is structurally related to several hindered phenol antioxidants also involved in the HPV program, notably CAS 2082-79-3, CAS 6683-19-8 and 32687-78-8 (these chemicals are also sponsored by Ciba Specialty Chemicals Corporation). Testing for these substances has demonstrated that the compounds are not developmental toxicants. Additional supporting data relating to hindered phenol antioxidants has been presented for the HPV Hindered Phenol Category, sponsored by the American Chemistry Council. These data indicate a low concern for developmental effects.

REPRODUCTIVE TOXICITY *(Revised)*

Test substance: Thiodiethylene bis (3,5-di-tert-butyl-4-hydroxyhydro cinnamate)
CAS No. 41484-35-9

The requirement for reproductive toxicity testing is met by the availability of 90-day repeat-dose testing with appropriate analysis of reproductive organs. This summary describes the available repeat dose testing.

Three repeat dose studies are available (see section 5.4 for details of testing):

- 3 Month Toxicity Study in Rats, Final Report, July 4, 1984. GU project no. 820112, Ciba Geigy Limited, Basel, Switzerland.
- 90-day sub-acute oral toxicity study in albino rats, Final Report, 19 December 1973. IBT No. 622-03561, Industrial BIO-TEST laboratories, Inc., Illinois.
- 90-Day sub-acute oral toxicity study in Beagle dogs, IBT No. 651-03562, December 1973. Industrial BIO-TEST laboratories, Inc., Illinois.

Reproductive organs were analysed in the 90-day repeat dose studies with rats and dogs cited above. Treatment-related adverse effects on reproductive organs were not observed in these studies. The details of reproductive organs from these studies are summarized below.

1. Study No. 820112, 1984

In this 3-month oral toxicity study in rats, all major organs were examined grossly and microscopically. In the following table, reproductive organ weights and ratios are presented. Statistical analysis of both absolute organ weights and organ to bodyweight ratios did not reveal any treatment-related effects.

Gross necropsy and histopathological examination showed that reproductive organs were comparable among all treatment groups. Testes, epididymis, uterus, and ovary were examined.

Table 1

Mean Organ Weight and Ratios

Male Rats

ORGANS	DOSE IN PPM									
	0.0		60.0		200.0		600.0		2000.0	
	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN
Body	20	469.079	20	466.364	19	475.399	20	480.414	20	485.079
Brain	20	2.444	20	2.462	20	2.448	20	2.415	20	2.449
Brain / Body	20	0.529	20	0.533	19	0.518	20	0.507	20	0.510
Gonads	20	3.649	20	4.005	20	4.041*	20	4.048*	20	4.146*
Gonads / Body	20	0.784	20	0.868	19	0.853	20	0.850	20	0.863
Gonads / Brain	20	149.165	20	163.055	20	165.401*	20	168.018*	20	169.600*

Female Rats

ORGANS	DOSE IN PPM									
	0.0		60.0		200.0		600.0		2000.0	
	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN	NO.	MEAN
+Body	20	288.155	20	290.864	20	287.904	20	290.679	18	281.688
+Brain	20	2.267	20	2.263	20	2.303	20	2.283	19	2.252
Brain / Body	20	0.792	20	0.785	19	0.804	20	0.792	18	0.805
+Gonads	20	0.183	20	0.169	20	0.162	20	0.201	19	0.182
Gonads / Body	20	0.064	20	0.059	20	0.057	20	0.070	18	0.065
Gonads / Brain	20	8.099	20	7.520	20	7.084	20	8.836	19	8.124

NO. = NO. OF VALUES/GROUP

* = SIGN. DIFFERENCE (LOCATION AND/OR DISPERSION) BETWEEN CONTROL (GROUP 1) AND GROUP X (SIGN. L. = 0.050)

2. Study No. 622-03561, 1973

In a 90-day subchronic toxicity study in rats, all surviving rats following 90 days of feeding were sacrificed and autopsied. At the time of gross examination a complete set of organs and organ tissues were removed from each rat and examined.

Microscopic examination of testes, seminal vesicle, ovary, and uterus were carried out both in control and the 10000 ppm groups. No outstanding differences were noted between test and control rats.

Organ weight and ratio data of gonads is given below.

Table 2

Organ weight and ratio data (mean values)
Organ: Gonads

Dose (ppm)	Organ Weight		Organ/ Body Weight Ratio (g/100 g)		Organ/ Brain Weight Ratio (g/ g)	
	Males	Females	Males	Females	Males	Females
0	3.261	0.077	0.6338	0.0272	1.5121	0.0395
1000	3.325	0.084	0.6550	0.0301	1.5259	0.0417
3000	3.420	0.086	0.6438	0.0304	1.5965	0.0427
10000	3.393	0.076	0.6689	0.0280	1.5596	0.0389

3. Study No. 651-03562, 1973

In a 90-day subchronic toxicity study in beagle dogs, at dietary levels of 10000, 20000, and 30000 ppm, no significant abnormalities were found in body weights, mortality, organ weights, blood chemistry, and gross and histopathological examination.

Organ weight and ratio data of gonads is given below.

Table 3

Gonad weight and ratio data

Dose (ppm)	Organ Weight (g)		Organ/ Body Weight Ratio (g/1000 g)	
	Males	Females	Males	Females
0	16.8	0.907	1.69	0.086
	23.0	0.781	2.23	0.078
	18.9	0.779	1.45	0.092
	18.2	0.773	1.54	0.090
10000	11.6	0.753	1.12	0.084
	25.7	0.961	1.76	0.092
	13.4	1.004	1.25	0.100
	22.4	1.077	1.52	0.095
20000	15.7	0.456	1.38	0.059
	13.0	0.644	1.29	0.076
	20.1	0.830	1.69	0.078
	18.3	1.003	1.45	0.086
30000	20.4	0.756	1.85	0.072
	11.2	0.451	1.10	0.047
	13.1	0.154	1.39	0.013
	20.5	0.861	1.52	0.084

All major tissues and organs were examined grossly. The weights of the liver, kidneys, spleen, gonads, heart and brain were recorded. Histopathological examination was done on gonads, uterus etc. No significant differences were noted between control and test groups.

One male at the highest dietary level (10,000 ppm) showed mild atrophy of the testes. There was no other significant difference between treated and control animals. There is no proof that the atrophy noted is related to test material.

Overall Conclusion: In three 90-day subchronic studies covering both rats and dogs there were no apparent treatment-related adverse effects on reproductive organs.